	PMTA REQUIREMENTS - Costs based on estimated internal NJOY hours at FDA's $65 estimated average rate + estimated external $ costs	Combined $000	Upper bound estimate
VI	CONTENT OF A PREMARKET TOBACCO PRODUCT APPLICATION FOR ENDS PRODUCTS	1,393	3,236
A	GENERAL INFORMATION	11	11
B	TABLE OF CONTENTS	0	0
C	DESCRIPTIVE INFORMATION	1	1
D	PRODUCT SAMPLES	0	0
E	LABELING	3	3
F	ENVIRONMENTAL ASSESSMENT	23	23
G	SUMMARY OF ALL RESEARCH FINDINGS	63	63
H	SCIENTIFIC STUDIES AND ANALYSES	1,293	3136
1	*Product Analyses and Manufacturing - full reports of all testing including where applicable:*	232	*232*
	Source data (3 different batches with minimum 10 replicates per batch, with date and time sampling points)	29	29
	Accreditation information for each testing laboratory	0	0
	Validation information & rationale for selecting each test method, including any relevant voluntary testing standards	0	0
	Complete descriptions for any aerosol-generating regimens used for analytical testing	0	0
1a	**Components, ingredients & additives**	94	94
	Provide a complete list of uniquely identified components, ingredients, and additives by quantity, the applicable specifications, and intended function for each.	1	1
	List information regarding the container closure system	1	1
	Provide a complete list of uniquely identified constituents including testing for those listed in guidance (29 constituents), other toxic chemicals contained or delivered, from leaching, aging, in aerosol from heating, tested in a range of conditions under which the user may use the product including intense and non intense use conditions. Test a range of liquids in a specific device and for a specific liquid test with a range of devices	51	51
	Report the pH of the liquids and the resulting aerosol		
	Submit information regarding any voluntary standards with which the product complies, why the standard is relevant, as well as testing to demonstrate conformance.		
	VIII .A. AEROSOLIZING APPARATUS (ADDITIONAL RECOMMENDATIONS): provide info in this section and in addition, discussions on the following		
	Aerosolizing apparatus features, material & ingredient functions, capabilities to monitor product performance (e.g. temperature sensing, voltage sensing, battery life detection) instructions and method of operation, materials of apparatus compnents, operating ranges, power supply type, charging source and safety of using different charging sources, and heating source (e.g. coil, chemical reaction).		
	Detailed apparatus schematics - e.g. CAD drawings - dimenstions, pictures, labeling, engineering design parameters.		
	Electricial safety & applicable standards to which conformance have been demonstrated. Descriprtion of all built in electrical safety features. If a controller contained then list and discuss the power management techniques such as pulse width modulation or direct current.		

	VIII. B.1. Batteries: Amperage, mAh rating, type, voltage output at full and low charge, testing certificates. Voltage range and wattage range if gthe apparatus alters or regulates the voltage. If alarm capabilities info if includes: reverse polarity protection, under voltage lock out protection, over voltage lock out protection, low resistance protection, high controller temperature protection, unintended activation protection. VIII.B.2. Atomizers: Draw resistance, operating range, e-liquid capacity, aerosol particle size across operable range. Coils: number of coils, gauge and material, coil resistance, coil falure testing. Wick: ignition temperature, wicking absorbency (if refillable test with low and high viscosity eliquids)	19	19
	VIII.B.3. Software: software descriptionincl summary of the features and operating environment, hazard analysis of hardware/software hazards including severity assessment and mitigations, software requirements specification including a summary of functional requirements. Traceability analysis among requirements, specifications, identified hazards and mitigations, and verification and validation testing. Verification and validation documentation, including software functional test plan, pass/fail criteria and results, and a recision level history, including revision history log with reelase version number and date.	incl	
	VIII FOR ELIQUIDS: in addition, provide adequate information to characterize the constituents and other chemical constituents (e.g. menthol, glycerin) in the eliquid and dentify charactersitics of the liquid that may impact constituents in the aerosol. Provide e-liquid design parameters that would be affected by abd would affect aerosolizing apparatus performance, such as the e-liquid viscosity and boiling point.	incl	
1b	Properties	60	60
	Description of product dimensions and overall construction of the product (using a diagram or schematic drawing that clearly depicts the finished product and its components with dimensions, operating parameters, and materials.	2	2
	Description of all design features of the product, specifying the explicit range of or the nominal values of the design features & design tolerance	4	4
	Quantitative description of the performance criteria	15	15
	Description of container closure system - protect, preserve, from damage, environmental contaminants, leaching, migration of constituents into products.	1	1
	Description of how the product's properties differ from similar marketed tobacco products in the same category	2	2
	Storage and stability information - shelf lif, changes in pH, HPHCs & other toxic chemicals over the lifespan, how affected by storage conditions such as moisture, temperature, full reports of stability testing, how the performance may decline	34	34
	Assessments of product design hazards that could be expected to result in illness or injury from normal use and foreseeable misuse of the product incl mitigation	3	3
1c	**Principles of operation**	2	2
	Full narrative description of the way in which a consumer will use the product including operation, how a consumer could change the cproduct characteristics, adjust the performance, or add or subtract ingredients. Also other types of ENDS products with which the product can be used.	2	2
1d	Manufacturing	47	47
2	*Nonclinical and Human Subject Studies*	1,062	*2904*
	Include investigations that support the PMTA but also investigations that do not support or are aversive to the PMTA.		

Provide information on both nonclinical and clinical investigations incl but not limited to studies assessing constituents of tobacco, smoke, aerosol, toxicology, consumer exposure and consumer use profiles.

Information on investigations concerning products with novel components, ingredients, additives, or design features that are similar or related to the product and investigations concerning products that share novel components, ingredients, additives, or design features with the product.
Indicate source of funding for all studies and a statement re any potential conflicts of interest.
Include all information from investigations both within and outside the United States.
Bibliography and full article for each study in a literature review - how reviewed, include full study reports and data studies self conducted or conducted on your behalf.

2a	**Nonclinical health-risk information**	244	537
	Provide a thorough toxicological and pharmacological evaluation of each of the ingredients, mixture of ingredients, and aerosols produced by the product.	82	382
	Toxicology data from the literature	20	20
	Analysis of constituents & other toxicants under both intense and non-intense use conditions		
	in vitro toxicology studies (e.g. genotoxicity, cytotoxicity)	62	62
	In vivo toxicology studies (to address unique toxicology issues that can't be addressed by alternative approaches).	0	300
	Computational modeling		
	Thorough literature review including publicly available toxicology databases incl description of search methodology, all publications related to the tox eval of each of the ingredients and the mixture in the e-liquid and aerosol produced.	51	51
	Info re oral, inhalation, dermal, ocular routes of exposure.		
	Extractable leachable information from aerosolizing apparatus	51	51
	Tox endpoints such as cytotoxicity, genotoxicity, respiratory, cardiac, reproductive, and developmental toxicity.		
	Hazard identification studies		
	Exposure kinetics, metabolism. Deposition and elimination profile when available		
	Conclusion as to whether there is a toxicological concern re the ingredients, constituents, flavors, humectants, and mixtures of humectants that will be delivered in the aerosol from use.		
	Information on physiochemical changes of the mixture of ingredients in your product due to temperature, wattage, and/or voltage changes, if available.		
	Studies might be conducted if unable to acquire publicly available toxicology information for specific aerosol ingredients.		
	Based on potential human exposure - highest and lower exposure level.		
	Effect of change in voltage/temperature if variable by user		
	Aerosolization properties of ingredients, particle size, deposition of particles. How these properties could affect tox profile.		

	In vitro assays to evaluate genotoxic potential v other tobacco products - condicted with multiple concentrations of product.		
	V11 B. FLAVORS: scientific review including toxicological review on flavor additives should be included in a PMTA for an e-liquid. Under section 910(b)(1)(A) of the FD&C Act, you must include as full reports of all information published or known, or reasonably known to you concerning investigations that have been made to show the health risks of the product and whether the product presents less risk than other tobacco products. FDA considers the appeal and use of ENDS product flavors important to ascertain the health risks of these products. Describe research on flavor development including, but not limited to market segmentation analysis or sensory testing. Describe consumer perceptions among current ENDS users and other tobacco users for appeal and use intentions based on labeling and actual use of flavors and product design.	103	103
2b	**Human health impact information**	817	2366
	Characterize the likely impact of the product on the health of both users and nonusers of tobacco products to support thaat marketing the product would be appropriate for the protection of the public health. To evaluate acute and chronic health effects associated with the product, FDA recommends including studies, other scientific evidence ot both that identify biomarkers of exposure (e.g. NNAL, NNN), biomarkers of harm, and health outcome measurements or endpoints.		
2bi	***Consumer perceptions***	101	101
	Evaluations should address how consumers perceive product risk. Both absolute and in comparison to other categories of products as well as to quitting all tobacco use. Include the use intentions among current ENDS users, non users, and other tobacco product users, as well as reasons for use (e.g. complete substitution, use in environments where smoking is not allowed		
	Published reports and data on consumer perceptions of the product and its packaging		
	Data on consumer perceptions of the harms of the product and of its proposed labeling or advertising		
2bii	***Likelihood of initiation and cessation by both users and nonusers of tobacco products***	51	600
	Published literature or sponsor-initiated studies evaluating the effects of the product on users and nonusers, including effects on initiation, switching behavior, cessation, and dual use. If product not the same, justify why such a comparison is appropriate.		
	Scientific information on the likelihood of product use by youth, young adults, pregnant women, and other vulnerable populations		
2biii	***Product use patterns***	203	703
	Consider topography of how individual users consume the product (No puffs, puff duration, puff intensity, duration of use), frequency with which consumers use the product, trends of consumption over time, switching and cessation rates for users of the product, potential for use in conjunction with other tobacco products (dual use). Data should be broken down by demographic factors (age, sex, ethnicity, education and by geographic regions.		
	Share marketing plan for FDA to better understand the potential consumer demographic. If currently marketed, share sales data by population demographic factors and tobacco use status. Analyze in 4-week or monthly intervals if available and include: Product code, total US sales in dollars, units, and volumem breakdowns by US census region, major retail markets and channels where sold, promotional discounts. Information on top selling brands as a comparison for all recommended information.		
2biv	***Labeling comprehension, self-selection, and actual use***	61	61

	Include studies demonstrating that users and nonusers understand the product's labeling and instructions for use, and use the product according to its labeled instructions. Provide a description of how the product is actually used by the consumer, including both use as intended and as not intended.		
2bv	***Human factors***	43	43
	Identify risks associated with real world use of the product and demonstrate that potential risks associated with use for users and non users have been mitigated. Normal use, foreseeable misuse conditions; use environment sucha s home , community, mobile environments (forms of transportation) use-related hazards and estimated error risk (including misuse); risk controls to ensure harms and unintended consequences are minimized, and adverse experiences.		
2bvi	***Abuse liability***	328	328
	Abuse liability evaluations including pharmacokinetic evaluations should consider the addictiveness and abuse and misuse potential of the product and the exposure to nicotine during product use.		
	Published reports and data describing the abuse potential of the e-liquid and aerosolizing apparatus independently as well as when the products are used together, as it relates to other tobacco products.		
	Published reports and pharmacokinetic data(including published reports) examining the exposure to nicotine during use.		
2bvii	***Biomarkers of harm and biomarkers of exposure***	11	11
	Published reports or data on biomarkers of harm, biomarkers of exposure (e.g. NNAL, and NNN), and/or other immediate health outcomes to users and nonusers.		
2bvii	***Health outcomes***	21	521
	Data to support the impact of the new product on the health of users and nonusers including health effects related to specific constituents identified in the aerosol - including health effects of exposures. Conduct studies to ensure, to the extent possible that the finding are generalizable to the US populaiton of users and non-users of the product. Reliance on published reports must be justified by bridging to the product and appropriateness re impact on the US population.		
	including changes in physiological measurments, such as heart rate and blood pressure		
	changes in lung, cardiac, and metabolic function		
	adverse experiences, such as throat irritation and cough		
	changes in laboratory values such as mediators of inflammation and complete blood count indices		

Human Decision Making About Tobacco Products

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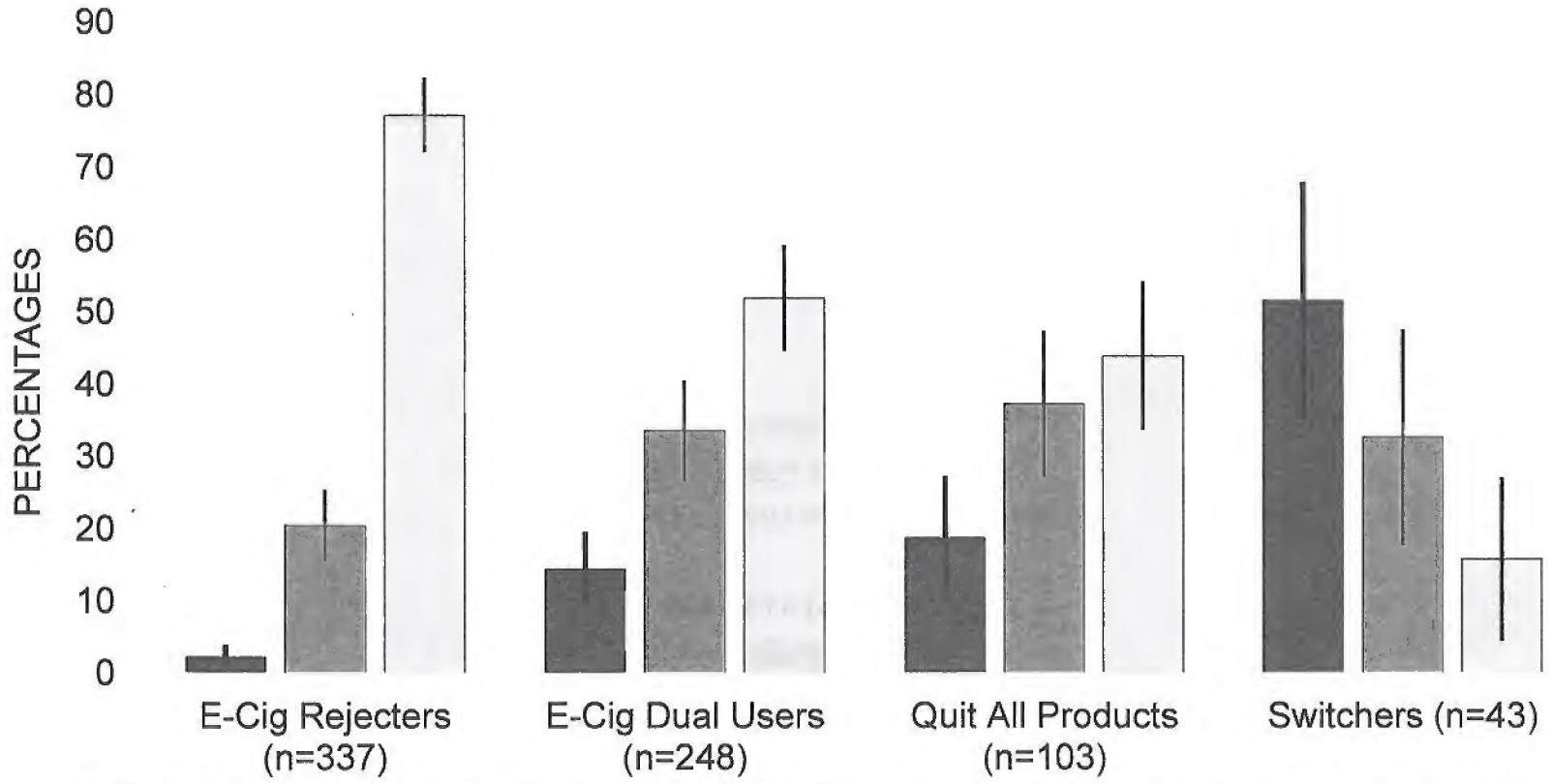
Experience of using e-cigarettes compared to smoking regular cigarettes



Unpublished data 2014 GSU Tobacco Products and Risk Perceptions Survey

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